Course of Bronchial Hyperresponsiveness in Patients With Occupational Asthma Caused by Exposure to Persulfate Salts

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OBJECTIVE: Persulfate salts are among the most frequently implicated causes of occupational asthma. The aim of this study was to describe the course of bronchial hyperresponsiveness and immunologic test results in patients with occupational asthma due to persulfate salts.

PATIENTS AND METHODS: Ten patients with occupational asthma due to persulfate salts were studied. Diagnosis was based on specific bronchial challenge tests performed at least 3 years before enrollment. An exhaustive medical and work history was taken during interviews with all patients, and all underwent spirometry and nonspecific bronchial challenge testing. Total immunoglobulin E levels were determined and skin prick tests to several persulfate salts were performed.

RESULTS: At the time of evaluation, 7 patients had avoided workplace exposure to persulfate salts. The bronchial hyperresponsiveness of 3 of those 7 patients had improved significantly. No improvement was observed in patients who continued to be exposed. Specific skin prick tests became negative in 3 patients who were no longer exposed at the time of the follow-up evaluation. Most of the patients continued to report symptoms, although improvements were noted. One patient, however, reported worsening of symptoms in spite of avoidance of exposure.

CONCLUSIONS: Although asthma symptoms and bronchial hyperresponsiveness may persist for patients with occupational asthma due to persulfate salts, their condition seems to improve if they avoid exposure. This course does not seem to differ from that reported for other cases of occupational asthma.

Key words: *Methacholine. Skin prick test. Follow-up monitoring. Rhinitis. Hairdressers.*

Evolución de la hiperrespuesta bronquial en pacientes con asma ocupacional por exposición a sales de persulfato

OBJETIVO: Las sales de persulfato son uno de los agentes más frecuentemente implicados en el origen del asma ocupacional (AO). El objetivo de este estudio ha sido establecer la evolución de la hiperrespuesta bronquial y de las pruebas inmunológicas en pacientes con AO por persulfatos en función de que persista o no la exposición a dichas sales.

PACIENTES Y MÉTODOS: Se estudió a 10 pacientes con AO por exposición a sales de persulfato, diagnosticados con prueba de provocación bronquial específica, en los que como mínimo habían transcurrido 3 años tras el diagnóstico. En todos los casos se realizaron un exhaustivo interrogatorio clínico y laboral, espirometría forzada y prueba de provocación bronquial inespecífica con metacolina, se determinaron los valores de inmunoglobulina E total y se practicaron pruebas cutáneas con las distintas sales de persulfato.

RESULTADOS: En el momento del control evolutivo, 7 pacientes habían abandonado la exposición a persulfatos. De los pacientes con hiperrespuesta bronquial positiva que habían abandonado el trabajo, se observó una mejoría significativa de ésta en 3 de ellos. Este hecho no se observó en ninguno de los pacientes que siguieron expuestos. La prueba cutánea específica se negativizó en 3 pacientes que no estaban expuestos en el momento del control evolutivo. Desde el punto de vista clínico, la mayoría de los pacientes continuaron presentando síntomas, aunque éstos habían mejorado, excepto en un caso en que, a pesar de evitar la exposición, empeoraron.

CONCLUSIONES: Aunque pueden persistir los síntomas de asma y la hiperrespuesta bronquial positiva, la evolución de los pacientes con AO por persulfato parece ser favorable si se evita la exposición. Esta respuesta no parece diferir de la comunicada en otros casos de AO.

Palabras clave: *Metacolina. Prueba cutánea. Seguimiento. Rinitis. Profesionales de peluquería.*

Introduction

Occupational asthma is the most common workplace disease in developed countries and accounts for between 30% and 60% of all work-related respiratory problems

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according to various voluntary case registries.[1-3] These databases indicate that isocyanates are the agents most often implicated, although substances such as flours, latex, and persulfate salts are gaining importance as triggers of occupational asthma.[4-6] In fact, exposure to persulfate salts is now thought to be the cause of 12% of the cases in Catalonia, Spain, where it is the second leading cause.[5] In spite of this high estimated incidence attributable to this agent, to date, only 4 case series have been published with the purpose of elucidating the clinical characteristics of this entity[7-10] and only one of them followed the patients after diagnosis.[9]

Avoidance of contact with the agent responsible for triggering occupational asthma is generally considered the best measure to take.[11] However, a recent systematic review of the literature published with the aim of understanding the course of the disease in asthma patients who avoided contact after diagnosis showed that only 32% experienced clinical improvement.[12] Bronchial hyperresponsiveness continues to be high in 70% to 74% of those who avoid exposure to the trigger.[12]

In the case of bronchial hyperresponsiveness to persulfate salts, little is known of how patients fare once contact ceases, as no follow-up studies have been published. Our main purpose in this study was to assess changes in bronchial hyperresponsiveness in patients diagnosed with occupational asthma due to persulfate salts in relation to whether exposure is continued or not. We also observed how immune response changed in these patients.

Patients and Methods

Study Population

Ten of the 11 patients diagnosed with occupational asthma in a specialized respiratory clinic in a tertiary-level hospital were studied prospectively between 1997 and 2002. The patients were women with a mean (SD) age of 38 (9.7) years (range, 24-52 years) at the time of diagnosis, after which at least 3 years had passed before the follow-up visit of this study. Three patients were employees of a cosmetics factory where they mixed persulfate salts with other chemical agents to manufacture hair bleaches. The remaining 7 patients worked in beauty salons as hairdressers. They were exposed to persulfate salts when mixing such products with hydrogen peroxide to form a paste, which they then applied to hair. None of the women had asthma or a history of respiratory symptoms before starting those jobs. The clinical characteristics of 7 of the patients have been published previously.[9]

The ethics committee of our hospital approved the study and written informed consent was obtained from all patients.

Diagnosis of Occupational Asthma Due to Persulfate Salts

In all cases the diagnosis of occupational asthma triggered by persulfate salts was based on a specific bronchial challenge test carried out according to procedures proposed by our group for use in work-related asthma of this type.[13] Briefly, on the first test day 5 g of persulfate salt was mixed with 150 g of lactose and the patient transferred the mixture from one tray to another in a challenge chamber for 10 minutes. If the text was negative, the amounts of persulfate salt mixed with lactose increased from 10 g to 15 g to 30 g over the following days. Forced expiratory volume in 1 second (FEV_1) was measured every 10 minutes during the first hour after exposure and then once every hour. The test was considered positive when there was a fall in FEV_1 greater than 20% from baseline, provided there had been no change in that volume when the patient was exposed to lactose the day before the first challenge test.

A complete medical history, including an exhaustive employment history, was taken in an interview with each patient. The test battery included the following: spirometry with a bronchodilation test, monitoring of peak expiratory flow, measurement of total serum immunoglobulin (Ig) E (in peripheral blood), skin tests to common aeroallergens and to ammonium and potassium persulfate salts, and a nonspecific bronchial challenge with methacholine.

Follow-up Evaluation

Between January and July 2006 follow-up visits were made with all patients who agreed to participate in the study. That visit included a clinical interview and exhaustive employment history, spirometry, a nonspecific bronchial challenge test with methacholine, measurement of total serum IgE concentration, and skin tests with persulfate salts.

Symptoms and employment history. All patients were interviewed systematically about the presence of wheezing, cough, sputum production, dyspnea, and chest tightness. Scores from 0 to 5 were recorded for each symptom in accordance with the level of discomfort felt during the last year. A mean score was then calculated; 0 indicated absence of asthma symptoms whereas 5 indicated symptoms that were often incapacitating, as has been described for other diseases.[14] In addition, disease severity was classified according to lung function tests and the use of β_2-adrenergic agonists to relieve symptoms, in accordance with the guidelines of the Global Initiative for Asthma.[15] Patients were also asked if they had rhinitis, conjunctivitis, or dermatitis, or if they continued to be exposed to persulfate salts. If they were no longer exposed, they were asked how long had passed since the last contact.

Spirometry. Lung volumes were measured with a Datospir 120 D spirometer (Sibel, Barcelona, Spain) using the guidelines of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).[16] Reference values for a Mediterranean population were used for comparison.[17]

Methacholine challenge test. Methacholine challenge was carried out according to the instructions of Chai et al.[18] Briefly, a dosimeter (Mefar MB3, Bovezzo, Italy) was set to deliver a dose to be inhaled in 0.6 seconds followed by a pause between doses tailored to the patient's needs. At intervals of 3 minutes, 5 inspiratory capacity maneuvers

TABLE 1
Clinical Characteristics of the Patients With Occupational Asthma Due to Exposure to Persulfate Salts at Diagnosis and at the Follow-up Visit[a]

	Diagnosis	Follow-up Visit
Age, y	37.6 (9.7)	42.8 (10.5)
Smoking, yes/no	3/7	0/10
Rhinitis, yes/no	8/2	7/3
Conjunctivitis, yes/no	3/7	3/7
Dermatitis, yes/no	4/6	4/6
Asthma symptom score	3.3 (1)	1.7 (1.5)
GINA class		
No asthma	0	2
Mild intermittent	0	2
Mild persistent	3	3
Moderate persistent	7	3
Total immunoglobulin E, kU/L	187.8 (208.9)	139 (199.2)
Skin tests to aeroallergens, +/–	3/7	ND
Skin tests to persulfate salts, +/–	5/5	2/5
FEV_1, % predicted	100 (9)	95 (11)
PC_{20}, mg/mL	4.24 (3.7)	6.02 (4.2)
Duration of exposure before diagnosis, y	17.2 (7.9)	–

Abbreviations: FEV_1, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; ND, not determined; PC_{20}, methacholine provocation concentration required to produce a decrease of >20% in FEV_1
[a]Data are expressed as mean (SD) or number of patients.

to inhale increasing concentrations of methacholine (from 0.003 mg/mL to 8 mg/mL) were performed during tidal breathing until a reduction in FEV_1 of more than 20% from the baseline value had been reached or until the patient had received the maximum dose. The concentration of methacholine producing a 20% decrease in FEV_1 (PC_{20}) was recorded in milligrams per milliliter. A test was considered negative if the PC_{20} was greater than 8 mg/mL, as stipulated by the European Respiratory Society.[19] A variation in PC_{20} of 3.2 times the value recorded at the first visit was considered to indicate a significant change in bronchial hyperresponsiveness.[20]

Immunologic tests. All but 1 patient also underwent skin tests with potassium and ammonium persulfate salts (Sigma-Aldrich Corporation, St Louis, Missouri, USA) as proposed by Pepys[21] and applied previously.[9,22] The patient who was not tested with these salts had experienced a severe anaphylactic reaction during diagnostic testing.[9] Persulfate solutions of 5% (wt/vol) in buffered saline were used in order to avoid acidity. Histamine and phosphate buffered saline were used as the positive and negative controls. Results were read after 15 minutes. A test was considered positive when the average of the largest and smallest diameters of a wheal was at least 3 mm greater than the size of the negative control. Histamine tests were positive in all patients. A change in sensitization was considered significant if a skin test to a substance that had been negative became positive, or vice versa, during the follow-up period.

Total serum IgE concentrations (UniCAP System, Pharmacia AB, Uppsala, Sweden) were measured. Results over 150 U/mL were considered elevated.

Statistical Analysis

Results are expressed as mean (SD) or percentages. Given the small patient sample, between-group comparisons were not carried out. To assess whether or not a variable had improved within a group, the nonparametric Wilcoxon test was used. Correlations between variables were analyzed with the Spearman correlation coefficient (ρ).

Results

Table 1 summarizes the clinical characteristics of the patients at the time of diagnosis and at the follow-up visit. All were advised to discontinue exposure to persulfate salts after diagnosis and were prescribed asthma therapy with β_2-adrenergic agonists and inhaled corticosteroids in accordance with the level of severity of disease. The mean time between the diagnostic and follow-up visits was 62.8 (19) months (range, 39-101 months). Seven patients had changed

TABLE 2
Changes in Symptoms, Immunologic Tests, and Bronchial Hyperresponsiveness in Patients With Asthma Due to Exposure to Persulfate Salts

Case	Exposure at Follow-up Visit	Duration of Exposure Since Diagnosis, mo	Asthma Symptoms		Skin Test to Persulfate Salts		Total IgE, kU/L		FEV_1, %		PC_{20}		Change in PC_{20}[a]
			D	LV	D	LV	D	LV	D	LV	D	LV	
1	No	0	5	4	–	–	182	217	2.68 (99)	2.30 (91)	0.36	1	↑ 2.7
2	No	2	3	4.2	–	+	203	86	1.87 (79)	1.68 (74)	0.06	2.75	↑ 45.8
3	No	3	2.2	0	+	–	25	31	2.62 (98)	2.72 (105)	>8	>8	1
4	No	6	3.6	1	+	–	509	193	3.45 (105)	3.32 (101)	0.06	>8	↑ 13.3
5	No	2	4	0.6	+	–	342	134	3.47 (108)	3.29 (105)	1.89	>8	↑ 4.2
6	No	8	2.2	0	–	–	17	15	2.41 (99)	2.53 (106)	>8	>8	1
7	No	0	4.2	2.6	–	–	8	10	3.36 (94)	2.84 (81)	>8	>8	1
8	Yes	69	3.6	2	+	ND	32	29	2.70 (107)	2.32 (95)	1.5	4	↑ 2.6
9	Yes	49	2.8	1.8	+	+	541	662	3.85 (106)	3.54 (100)	6.5	5.75	↑ 1.1
10	Yes	45	2.2	0.8	–	–	19	13	3.30 (102)	2.86 (93)	>8	0.19	↓ 42.1

Abbreviations: D, diagnosis; FEV_1, forced expiratory volume in 1 second; IgE, immunoglobulin E; LV, last visit; ND, not determined; PC_{20}, methacholine provocation concentration required to produce a decrease of >20% in FEV_1.
[a] ↑ indicates increase; ↓, decrease.

jobs and were no longer exposed to persulfate salts. The mean time between diagnosis and last contact for these patients was 3 (3) months (range, 0-8 months). Three patients were still employed as hairdressers in their usual places of work, although they no longer carried out tasks that brought them into contact with persulfate salts. The mean time of follow-up for these 3 patients was 54.3 (12.8) months (range, 45-69 months).

Table 2 shows changes in the presence of symptoms, results of skin tests to persulfate salts, total serum IgE concentration, FEV_1, and PC_{20} to methacholine for each patient. Five of the 7 who had changed employment had a PC_{20} greater than 8 mg/mL at the follow-up visit. Two were considered cured as they had no symptoms and required no treatment, 2 had mild intermittent asthma, only 1 occasionally required β_2-agonists on demand, and 1 reported symptoms (positive symptom score) and needed chronic inhaled corticosteroid treatment. The 2 patients with a positive methacholine challenge tests in spite of having left their place of work had moderate persistent asthma and routinely required therapy with inhaled corticosteroids and long-acting β_2-agonists.

One of the 3 patients who continued to be exposed to the asthma trigger had a nonsignificantly higher PC_{20}, while the other 2 had lower PC_{20} values (significant in one of them). Three had persistent asthma symptoms, mild in 2 cases and moderate in 1. All required routine inhaled corticosteroid therapy to control symptoms.

The skin test became negative in 3 patients who had changed jobs. One patient who initially had a negative skin test had a positive result at the follow-up visit in spite of avoiding exposure to persulfate salts.

We found no significant differences in total IgE concentrations, FEV_1, or PC_{20} between diagnosis and the last follow-up visit in either of the 2 groups of patients. However, significant improvements in symptoms were found in the group of patients who had avoided exposure after diagnosis (P=.042). Analysis of the correlation between persistence of symptoms and age, time of exposure, latency period, and diagnostic delay showed a weak correlation for the last variable (ρ=0.413).

Discussion

The results of this study seem to suggest that the prognosis for occupational asthma due to persulfate salts is favorable if exposure is avoided. This finding is important because exposure to this substance is becoming one of the most important asthma triggers in the workplace.[4,5] However, the apparently favorable prognosis should be qualified. Although the symptoms of our patients who avoided exposure improved significantly, only 2 could be considered cured; symptoms persisted in the others with varying degrees of intensity. A large number of patients with occupational asthma due to a variety of triggers are known to continue to have asthma for many years after exposure no longer occurs.[23] Factors that contribute to the perpetuation of disease seem to be a longer duration of exposure before the appearance of symptoms; diagnostic delay, with a long symptomatic period prior to diagnosis; and finally the intensity of symptoms at the time of diagnosis.[24-26] An effect of smoking, or of age, on recovery is uncertain, although other authors have found that symptoms are more persistent in older patients.[27,28] In our study of a small group of patients, we only observed a weak correlation between persistence of symptoms and diagnostic delay.

Most authors seem to agree that patients with occupational asthma fail to improve in spite of treatment if they remain exposed, although few such patients have been studied.[29,30] The symptom scores improved for our 3 patients who were still in contact with persulfate salts, but the change was not significant and the classification of severity of disease remained the same. Two continued to have mild persistent asthma and the third, moderate persistent asthma. The course of disease in these patients contrasts with our observations for patients with asthma due to isocyanates, in whom disease clearly worsened in terms of both symptoms and functional class in all patients who did not avoid exposure,[31] consistent with the experience of Paggiaro et al[26] with the same type of occupational asthma.

All our patients who avoided exposure experienced improvement in bronchial hyperresponsiveness. In 3 of them, the improvement was significant (increase in PC_{20} of 3.2 times the value recorded during the previous challenge test). For 2 of these patients, a previously positive test became negative at the follow-up visit. Even though little has been established regarding the course of bronchial hyperresponsiveness in patients with occupational asthma due to persulfate salts who avoid exposure, observations in this clinical setting have been similar to those seen in asthma due to other workplace triggers. A systematic review of the literature by Rachiotis et al[12] showed that tests of bronchial hyperresponsiveness become negative in around 26% to 30% of patients with occupational asthma who avoid exposure. Recent studies suggest that this hyperresponsiveness lessens with time without exposure to the trigger, although the improvement is faster in the first 2.5 years after avoidance starts.[32] The factors that affect persistence and severity of bronchial hyperresponsiveness are as yet unknown, even if contact is avoided. Some authors have reported that good lung function and a high methacholine PC_{20} at the time of diagnosis are associated with a better prognosis.[33] Others, however, have found that improved bronchial hyperresponsiveness seems to be related to duration of exposure.[26,34-36] A recent study based on the analysis of the cellular components of induced sputum samples found that patients with persistent bronchial hyperresponsiveness have a higher level of bronchial inflammation than those whose tests become negative, and it was concluded that such inflammation is probably responsible for the persistence of bronchial symptoms.[37]

Just as there are few case reports on this type of asthma, there are likewise few clinical studies that follow patients over time in order to evaluate the course of hyperresponsiveness when the patient stays in contact with the agent that triggered the disease. Even though symptoms improved for our patients, 2 of the 3 patients still exposed had greater bronchial hyperresponsiveness, although the change was significant for only 1 of them. These results are similar to those reported

by Padoan et al[33] for patients with occupational asthma due to isocyanates, but different from those of Vanderplas et al[38] for patients with latex-induced asthma. In the patients of the latter group, PC_{20} was even seen to improve when exposure was reduced, even though some contact was maintained. Such differences in the course of bronchial hyperresponsiveness might be attributable to differential immunologic mechanisms at work with different triggers. Latex is a material with a high molecular weight and the reaction to it is probably IgE-dependent. Persulfate and isocyanate salts, on the other hand, have low molecular weights. Reactions may be related to other mechanisms that are more likely to perpetuate hyperresponsiveness even when there is less exposure to the trigger and that prevent a good response to medical treatment.

Finally, we did not generally observe lower IgE concentrations in patients who avoided exposure in comparison with those who maintained contact. However, it is interesting that 3 patients who had a positive skin test to persulfate salts at diagnosis became negative at follow-up. Such a switch was described recently by Park et al[39] in patients with occupational asthma caused by coloring agents. The meaning of this phenomenon in terms of clinical and functional course is uncertain. Although our patients with negative follow-up skin tests were nearly symptom-free at that time and their methacholine PC_{20} was over 8 mg/mL in all cases, that was not the case for the patients described by Park et al. In their patients, the course of bronchial hyperresponsiveness was unrelated to skin test conversion to negative. Similar observations, but in relation to specific IgE levels, were reported by Malo et al[40] in food industry workers and by Barker et al[41] in patients exposed to tetrachlorophthalic anhydride. Specific IgE titers decreased between diagnosis and follow-up in both those studies, especially during the first 2 years after exposure ended. The decrease did not appear to be related to clinical and functional course, however, consistent with what we and others have observed.

One of our patients whose skin test to persulfate salts, negative at diagnosis, became positive at follow-up had not been in contact with the trigger. This observation is difficult to explain. The initial test may have been a false negative, or it may be that persistent exposure to the antigen is not necessary for specific IgE antibodies to continue to be produced, as has been shown by Bice et al[42] in immune studies in dogs. In fact it is noteworthy that our patient with skin test conversion to positive was the only one who also experienced worsening of symptoms in spite of medical treatment and absolute avoidance of contact.

In conclusion, this study is the first to describe the course of bronchial hyperresponsiveness and immunologic tests in patients with occupational asthma due to exposure to persulfate salts. Although our patient series is small, our observations seem to indicate that the clinical and functional course for such patients will be favorable if they avoid exposure. That pattern of development is generally similar to the course of disease triggered by other agents,[12] in the sense that both asthma symptoms and the need for treatment to control them and bronchial hyperresponsiveness persist in 70% of patients with occupational asthma in spite of avoidance of the trigger.

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